

Ex. 4



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

APR 1 - 2014

Samuel S. Epstein, M.D.
Cancer Prevention Coalition
University of Illinois at Chicago
School of Public Health, MC 922
2121 West Taylor Street, Rm. 322
Chicago, Illinois 60612

RE: Docket Numbers 94P-0420 and FDA-2008-P-0309-0001/CP

Dear Dr. Epstein:

This letter is in response to your two Citizen Petitions dated November 17, 1994 and May 13, 2008, requesting that the Food and Drug Administration (FDA or the Agency) require a cancer warning on cosmetic talc products. Your 1994 Petition requests that all cosmetic talc bear labels with a warning such as "Talcum powder causes cancer in laboratory animals. Frequent talc application in the female genital area increases the risk of ovarian cancer." Additionally, your 2008 Petition requests that cosmetic talcum powder products bear labels with a prominent warning such as: "Frequent talc application in the female genital area is responsible for major risks of ovarian cancer." Further, both of your Petitions specifically request, pursuant to 21 CFR 10.30(h)(2), a hearing for you to present scientific evidence in support of this petition.

We have carefully considered both of your Petitions. We are committed to the protection of the public health and share your interest in reducing the risk of ovarian cancer. Current regulations state that cosmetic products shall bear a warning statement whenever necessary or appropriate to prevent a health hazard that may be associated with a product. FDA may publish a proposal to establish a regulation prescribing a warning statement on behalf of a petitioner if the petition is supported by adequate scientific basis on reasonable grounds.

After careful review and consideration of the information submitted in your Petitions, the comments received in response to the Petitions, and review of additional scientific information, this letter is to advise you that FDA is denying your Petitions. FDA did not find that the data submitted presented conclusive evidence of a causal association between talc use in the perineal area and ovarian cancer.

For this reason and for the additional reasons described below, FDA is denying your Petitions.

Plaintiff's Exhibit
No.

P-47

exhibits.ticker.com

Page 2 – Dr. Epstein

I. Discussion

The basis of your request, throughout both Petitions, can be summarized as comprising three major points:

1. Talc may be associated with asbestos.
2. Talc is a carcinogen based on the findings of a 1993 National Toxicology Program study.
3. Epidemiological studies confirm the causal relation between genital application of talc and ovarian cancer, and the protective effect of tubal ligation or hysterectomy, preventing the translocation of talc to the ovary.

As the points you raise in your Petitions concern the chemistry and toxicology of talc, the epidemiology associated with talc use, and the etiology of ovarian cancer, commensurate reviews were conducted to assess your request.

Chemistry Findings:

Asbestos is a known carcinogen and your first major point is that talc may be associated with asbestos. As evidence that talc cosmetic products contain asbestos, you first cite a 1968 survey of 22 talcum products that found fiber content averaging 19% in all 22 products. This author further concludes that “the fibrous material was predominantly talc but probably contained minor amounts of tremolite, anthophyllite, and chrysotile [asbestos-like fibers] as these are often present in fibrous talc mineral deposits ...”

You then cite a follow up study from 1971-1975 that examined 21 samples of consumer talcums and powder and concluded that cosmetic grade talc was not used exclusively in these products. This study found the presence of asbestiform anthophyllite and tremolite, chrysotile, and quartz. From these two citations, one may infer that currently available talc-containing cosmetic products are presently contaminated with asbestos, a known carcinogen. Unfortunately, you did not present any original data on the chemical composition of talc currently being used in cosmetics talc products or data linking these findings to currently used talc.

It has been reported in the scientific literature that most talc products in world trade are impure as a result of the geological processes involved in the formation of talc deposits. Further, talc containing asbestos fibers such as tremolite asbestos or chrysotile are sometimes encountered. However, large deposits of high purity, asbestos-free talc do exist and talc purification techniques have been developed which can be used to improve talc quality. Thus, while it has been reported in the past that cosmetic talc has been contaminated with asbestos, it has been also reported that asbestos-free talc deposits do exist. In addition, techniques do exist for the purification of talc in order to improve its quality. You have not provided evidence that asbestos contaminated talc-containing cosmetic products are currently being marketed, since the data submitted is almost 40 years old.

Page 3 – Dr. Epstein

Because safety questions about the possible presence of asbestos in talc are raised periodically, in 2009 FDA conducted an exploratory survey of currently marketed cosmetic-grade raw material talc and finished cosmetic products containing talc. This survey analyzed cosmetic-grade raw material talc from four suppliers out of a possible group of nine suppliers we had requested talc samples from, along with thirty-four talc-containing cosmetic products currently available in the Washington, D.C. metropolitan area for the presence of asbestos. In order to cover as broad a product range as possible, samples identified for testing included low, medium, and high priced products, along with some from “niche” markets. The cosmetic products identified as containing talc included eye shadow, blush, foundation, face powder, and body powder.

The survey found no asbestos fibers or structures in any of the samples of cosmetic-grade raw material talc or cosmetic products containing talc. While FDA found this data informative, the results were limited by the fact that only four suppliers submitted samples and by the number of products tested. They do not prove that all talc-containing cosmetic products currently marketed in the United States are free of asbestos contamination. As always, when potential public health concerns are raised, we will continue to monitor for new information and take appropriate actions to protect the public health. You may wish to see more on this survey on our website at <http://www.fda.gov/Cosmetics/ProductandIngredientSafety/SelectedCosmeticIngredients/ucm293184.htm>.

Toxicology Findings:

Your second major point is that talc is a carcinogen with or without the presence of asbestos-like fibers. The basis to this claim is that in 1993, the National Toxicology Program (NTP) published a study on the toxicity of non-asbestiform talc and found clear evidence of carcinogenic activity.

This NTP report concluded that cosmetic-grade talc caused tumors in animals, even though no asbestos-like fibers were found. The report made the following observations:

- There was some evidence of carcinogenic activity in non-asbestiform talc from inhalation studies in male rats based on an increased incidence of benign or malignant pheochromocytomas of the adrenal gland.
- There was clear evidence of carcinogenic activity of talc in female rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung and benign or malignant pheochromocytomas of the adrenal gland.
- There was no evidence of carcinogenic activity of talc in male or female mice exposed to 6 or 18 mg/cubic meter.

However, this study lacks convincing scientific support because of serious flaws in its design and conduct, including:

- The investigators used micronized talc instead of consumer-grade talc resulting in the experimental protocol not being reflective of human exposure conditions in terms of particle size.

Page 4 – Dr. Epstein

- Investigators conceded that they had problems with the aerosol generation system; whereby, the target aerosol concentrations were either excessive or not maintained during 26 of the 113-122 weeks of the study.
- The study did not include positive and negative dust controls which would have permitted an “exact assessment” of the talc’s carcinogenicity relative to the two control dusts.

In light of these shortcomings, a panel of experts at the 1994 ISRTP/FDA workshop declared that the 1993 NTP study has no relevance to human risk.

In addition, we reviewed relevant toxicity literature (consisting of 15 articles from 1980 to 2008), not cited in your Petitions, to determine if there was additional support at this point in time to for your suggested warning label. Scientific literature on studies of acute exposure effects, subchronic exposure effects, chronic exposure or carcinogenicity effects, developmental or reproductive toxicity, and genotoxicity effects were reviewed. As a result of the review of this relevant literature, FDA did not find enough additional support at this point in time for your suggested warning label.

Epidemiology and Etiology Findings:

Your third major point is that epidemiological studies confirm the causal relation between genital application of talc and ovarian cancer, and the protective effect of tubal ligation or hysterectomy, preventing the translocation of talc to the ovary.

After consideration of the scientific literature submitted in support of both Citizen Petitions, FDA found:

- 1 The exposure to talc is not well-characterized; it is not known if the talc referred to in the scientific studies was free of asbestos contamination; various consumer brands or lots of talc were not identified; and contamination of talc by asbestiform minerals or other structurally similar compounds was not ruled out.
- 2 Several of the studies acknowledge biases in the study design and no single study has considered all the factors that potentially contribute to ovarian cancer, including selection bias and/or uncontrolled confounding that result in spurious positive associations between talc use and ovarian cancer risk.
- 3 Results of case-controls studies do not demonstrate a consistent positive association across studies; some studies have found small positive associations between talc and ovarian cancer but the lower confidence limits are often close to 1.0 and dose-response evidence is lacking.
- 4 A cogent biological mechanism by which talc might lead to ovarian cancer is lacking; exposure to talc does not account for all cases of ovarian cancer; and

Page 5- Dr. Epstein

- 5 there was no scientific consensus on the proportion of ovarian cancer cases that may be caused by talc exposure.
- 6 The conclusion of the International Agency for Research on Cancer that epidemiological studies provide limited evidence for the carcinogenicity of perineal use of talc based body powder and the IARC classification of body-powder talc as group-2B, a possible carcinogen to human beings, is persuasive, but the results of the Nurses' Health Study, a large prospective cohort study, revealed no overall association with ever talc use and epithelial ovarian cancer.

Per the etiology review, approximately 10% of epithelial ovarian cancers are associated with inherited mutations. The remaining 90% of epithelial ovarian cancers are not related to these genetic mutations are non-hereditary. They have been historically classified based on histology as borderline/low malignant potential, serous, endometrioid, mucinous, and clear-cell.

Two theories have historically dominated on the cause of epithelial ovarian cancer and these are the “incessant ovulation hypothesis” and the “gonadotropin hypothesis.” In addition to these endogenous factors, the role of exogenous factors via retrograde transport of noxious substances (e.g. carcinogens, particulates such as talc and asbestos, endometriosis and infectious agents) from the vagina and uterus into the Fallopian Tubes and peritoneal cavity have been studied extensively as a possible risk factor for ovarian cancer.

While there exists no direct proof of talc and ovarian carcinogenesis, the potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable. It is, therefore, plausible that perineal talc (and other particulate) that reaches the endometrial cavity, Fallopian Tubes, ovaries and peritoneum may elicit a foreign body type reaction and inflammatory response that, in some exposed women, may progress to epithelial cancers. However, there has been no conclusive evidence to support causality.

The best evidence for an association or causal relationship between genital talc exposure and ovarian cancer comes from epidemiologic data which show a statistically significant but modest increased risk of epithelial ovarian cancer, especially with serous histology, among women with a history of genital dusting with talcum powder. While the growing body of evidence to support a possible association between genital talc exposure and serous ovarian cancer is difficult to dismiss, the evidence is insufficient for FDA to require as definitive a warning as you are seeking.

Request for hearing

In addition to your request for a warning label, you also requested a hearing, under 21 CFR 10.30(h)(2), so that you can present scientific evidence in support of your petitions.

Page 6 – Dr. Epstein

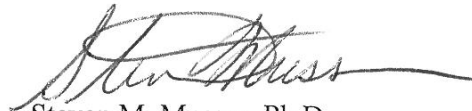
Under this regulation, FDA may deny a citizen petition request for a hearing if the data and information submitted (even if accurate), are insufficient to justify the determination urged. In consideration of your request, we conducted an expanded literature search dating from the filing of the petition in 2008 through January 2014. The results of this search failed to identify any new compelling literature data or new scientific evidence.

Since we find that the data and information are insufficient to justify the determination you request and we did not identify any new compelling literature data or new scientific evidence, FDA is also denying your hearing request.

II. Conclusion

FDA appreciates the goals of the Cancer Prevention Coalition and FDA supports the goal of reducing the rate of ovarian cancer. Although FDA is denying the Cancer Prevention Coalition's petitions for the reasons discussed above, the Agency shares your commitment to the public health.

Sincerely,

A handwritten signature in black ink, appearing to read "Steven M. Musser", with a long horizontal flourish extending to the right.

Steven M. Musser, Ph.D.
Deputy Director for Scientific Operations
Center for Food Safety
and Applied Nutrition

Drafted: J. Gasper, OCAC, 2/28/14
Comments: L. Katz, OCAC, 3/3/14
Revised: J. Gasper, OCAC, 3/4/14
Cleared: N.Sadrieh, OCAC, 3/4/14
Cleared: LMKatz, OCAC, 3/5/14
Reviewed: FHogue, OCAC: 3/6/14
Cleared by: Musser: 3/13/14
F/T: SRussell, OCAC 3/18/14